Paper 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KIM SVERKER IMMANUEL PETTERSSON
and TIMO NILS-ERIK LUVGREN

Appeal No. 2001-1412
Application No. 08/629,177[1]

ON BRIEF

Before: TORCZON, SPIEGEL and GARDNER-LANE, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 through 4, 7 through 17 and 20 through 54, which are all of the claims pending in this application. Claims 1, 2 and 15 are illustrative and are attached as an appendix to this decision.

The examiner relies upon the following references as evidence of obviousness:

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[1] Application for patent filed April 8, 1996.

Rutner et al. (Rutner)	4,256,725	Mar. 17, 1981
Freundlich et al. (Freundlich)	4,857,454	Aug. 15, 1989
Diamandis et al. (Diamandis)	5,089,423	Feb. 18, 1992
Deeg et al. (Deeg)	5,378,638	Jan. 3, 1995

Mair et al. (Mair), "Equivalent Early Sensitivities of Myoglobin, Creatine Kinase MB Mass, Creatine Kinase Isoform Ratios, and Cardiac Troponins I and T for Acute Myocardial Infarction," Clinical Chemistry, Vol. 41, No. 9, pp. 1266-1272 (September 1995).

Ohman et al. (Ohman), "Early detection of acute myocardial infarction: additional diagnostic information from serum concentrations of myoglobin in patients without ST elevation," British Heart Journal, Vol. 63, pp. 335-338 (1990).

Rabitzsch et al. (Rabitzsch), "Immunoenzymometric Assay of Human Glycogen Phosphorylase Isoenzyme BB in Diagnosis of Ischemic Myocardial Injury," Clinical Chemistry, Vol. 41, No. 7, pp. 966-978 (July 1995).

Xu et al. (Xu), "Simultaneous Quadruple-Label Fluorometric Immunoassay of Thyroid-Stimulating Hormone, 17"-Hydroxyprogesterone, Immunoreactive Trypsin, and Creatine Kinase MM Isoenzyme in Dried Blood Spots," Clinical Chemistry, Vol. 38, No. 10, pp. 2038-2043 (October 1992).

ISSUES[2]

Claims 1-4, 7-9, 15-17, 20-22, 28-34, 40-45 and 51-54 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Deeg in view of Rutner. Claims 14, 27, 39 and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Deeg in view of Rutner as applied to claims 1-4, 7-9, 15-17, 20-22, 28-34, 40-45 and 51-54 above, and further in view of Freundlich taken with each of Ohman, Mair and Rabitzsch. Claims 10-13, 23-26, 35-38 and 46-49 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Deeg in view of Rutner as applied to claims 1-4, 7-9, 15-17, 20-22, 28-34, 40-45 and 51-54 above, and further in view of Freundlich in view of Diamandis and Xu. We **reverse**

[2] According to the advisory action (Paper 22, mailed December 27, 1999), the examiner withdrew the final rejection of claims 1-4, 7-17 and 20-54 under 35 U.S.C. § 112, first paragraph, in view of appellants' RESPONSE AFTER FINAL (Paper 21, filed November 30, 1999).

all three rejections.

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's answer (Paper 28, mailed May 9, 2000) for the examiner's reasoning in support of the rejections and to the appellants' brief (Paper 27, filed April 20, 2000) for the appellants' arguments thereagainst.

THE INVENTION

Appellants' claimed invention is directed to immunoassays and devices comprising reaction wells containing all necessary reagents predried therein (specification, p. 1, ll. 1-5; p. 2, ll. 20-22; p. 5, ll. 2-4). An analyte specific component, e.g., an anti-analyte antibody **10**, is immobilized directly or indirectly (e.g., a biotinylated antibody **10** is bound to a streptavidin **13** coated well) onto the surface of the well (id., p. 8, ll. 9-15 and 20-23; Exs. 3 and 4; FIG. 1A and 1B). An "insulating" layer **11** containing carbohydrate and/or protein is dried on top of the immobilized component **10** (id., p. 8, ll. 15-18 and 23-24; p. 11, ll. 10-12; Ex. 5; FIG. 1A and 1B). Finally, a fluorescent-labeled analyte specific component, e.g., a lanthanide chelate labeled anti-analyte antibody **14** (for a non-competitive assay) or labeled analyte **14** (for a competitive assay) is added on top of the insulating layer **11** and dried (id., p. 3, ll. 22-24; p. 7, ll. 12-17; p. 8, ll. 18-20 and 24-26; p. 11, ll. 23-24; Ex. 5; FIG. 1A and 1B). To use, sample is added to the well and incubated; then the well is washed and immobilized label is measured to determine the amount of analyte in the sample (id., p. 5, ll. 11-31; p. 8, ll. 29-31; p. 10, ll. 12-31; Ex. 6). More than one analyte may be

determined per well if different labels (e.g., europium, terbium, samarium and dysprosium chelates) are used (id., p. 5, ll. 16-20).

According to appellants, the insulating antibody prevents the immobilized component from contacting the labeled component until sample is added to the well, thereby dissolving the insulating layer and allowing all components and analyte to contact one another (brief, pp. 4-5).

OPINION

To establish a prima facie case of obviousness, there must be some suggestion or motivation to modify the reference or combine reference teachings and reasonable expectation of success. Furthermore, the prior art must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Here, all of the claims on appeal require an analyte specific component immobilized on a surface of a reaction well in a single continuous region.

Deeg describes an analysis element (**device**) comprising a carrier layer with dried reagents and an isolating intermediate layer (**insulating layer**) prepared by "printing" the reagents on the carrier layer in discrete rows of continuous microdots using an ink-jet printer. As shown in Fig. 3, a first reagent set **A** of discrete rows **20, 22, 24, 26, 28** of biotinylated antibody **<TSH>!Bio** (**analyte specific component**) are immobilized via streptavidin **TBSA-SA** (**secondary immobilizing reagent**) onto a surface of a carrier layer **2**. An inert isolating substance, e.g., of bovine serum albumin and sucrose, is applied across the "hills" (rows of immobilized antibody) and "valleys" (open spaces between the rows) of the carrier layer **2** to form one continuous insulating

layer **5**. A second reagent set **B** of discrete rows **21, 23, 25, 27** of peroxidase-labeled antibody **<TSH>!POD** (**labelled analyte specific component**) is applied on top of the insulating layer **5** in the alternating "valleys" of the carrier layer **2**. [See Fig. 3; c. 2, l. 56 - c. 3, l. 26; c. 4, l. 46 - c. 5, l. 1; Example 1; c. 8, ll. 34-44.] Deeg further describes both enzymes and fluorescent markers as conventional labels in immunoassays (c. 6, ll. 26-29) and the use of protective and/or blocking layers of protein and sugar or protein to ensure storage stability of an immobilized binding partner, to prevent nonspecific binding of a mobilizable binding partner to the carrier layer **2** and to improve solubilization of a mobilizable binding partner (c. 6, ll. 12-37). Deeg still further describes the microcompartmentalization of the reagents made possible by ink-jet technology as permitting very short diffusion distances between reagents, relatively short reaction times, thorough mixing of the reagents without additional measures, and use of very small amounts of sample and reagent (c. 4, ll. 6-14; c. 7, ll. 36-39).

Rutner describes coating a substrate, preferably a polystyrene plastic test tube, with a labeled form of ligand, a receptor for the ligand and an ionic salt solution (c. 3, ll. 8-27); incubating, e.g., overnight or for 16 to 72 hours; aspirating; and drying in vacuo (Exs. 1-4). Rutner further describes radioisotopes, enzymes, and fluorescent materials as well known labels in the ligand-receptor art (c. 2, ll. 19-30).

According to the examiner,

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made that all of the assay components in the method of Deeg et al could be dried in the test wells prior to adding sample and that labels which would only require the addition of sample containing ligand for detection could be used, i.e., fluorescent markers,

> because Rutner et al. specifically disclose that the solid substrate containing the labeled form of the ligand and receptor are aspirated and dried in vacuo prior to use in the assay (column 4, lines 27-31) to provide for a one-step assay. One of ordinary skill in the art would have been motivated to dry all of the assay reagents in the assays taught by Deeg et al. and use fluorescent markers on the labelled binding partner because doing so would allow for a one-step efficient assay that could be used to detect large numbers of samples and the dried reagents would preserve better. The use of fluorescent markers in Deeg would eliminate the need for the addition of any reagents after the wash step. [Answer, pp. 5-6.]

First, the examiner has not pointed out, and we do not find, where Deeg discloses or suggests using a reaction/test well as a suitable substrate for applying reagents using an ink-jet printer. The examiner has not stated what she considers to be the reaction wells in Deeg or where appellants' specification defines "reaction well" as anything other than a conventional well, e.g., a well in a microtitration plate or a microtitration strip, as shown in appellants' Figs. 1A and 1B (see also specification, p. 3, l. 21; p. 5, ll. 12-13; p. 13, l. 12; p. 14, l. 17). Furthermore, although Rutner describes solid phase substrates as being "in particulate form, sheet form or in the form of a test tube" (c. 2, ll. 41-42), Deeg only describes "printing" reagents on one form, i.e., a sheet or "film" of plastic, using an ink-jet printer. The examiner has not established that it would have been within ordinary skill in the art to modify an ink-jet printer to "print" reagents inside a test tube or reaction well instead of on a carrier film or sheet.

Second, Deeg describes multiple discrete rows of each reagent not single layers of each reagent (brief, pp. 11-12), i.e., not an "analyte specific component [immobilized] ... in a single continuous region of said reaction well" as claimed. The examiner argues that "Deeg alternates reagent materials for the advantage of faster mix times upon

dissolution. One could forgo this advantage by maintaining only a single compartment for each reagent." (answer, p. 14). However, the proposed modification would negate "applying the ink-jet technique to produce compartments of different immunological reaction components arranged in alternation and spatially separated, but nevertheless close together" ... "which [compartmentalization] enables the binding reactions in question to proceed rapidly and homogeneously with a very small amount of sample and reagent and a high reaction binding rate" (Deeg, c. 7, ll. 25-29 and 36-39). It would also forgo the "very short diffusion distances between the reagents contained in different sets of compartments" which provides the "relatively short reaction times and thorough mixing of the reagents without special additional measures" in Deeg (c. 4, ll. 6-10). The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (Although a prior art device could have been turned upside down, that did not make the modification obvious unless the prior art fairly suggested the desirability of turning the device upside down.). Thus, the examiner's opinion that it would have been obvious to maintain only a single compartment for each reagent, standing alone, is simply a conclusion without an evidentiary basis.

Third, neither Rutner nor any of the remaining tertiary references (Freundlich, Diamandis, Mair, Ohman, Rabitzsch and Xu) make up for the deficiencies of Deeg. The examiner argues "that larger quantities of reagents could be used in conjunction with a different solid support known in the prior art, such as a microtiter plate or a test

tube which also reads on a reaction well and is specifically taught by Rutner..." (answer, pp. 13-14). However, while each of Rutner and the tertiary references disclose one or more individual part(s) of the claimed invention, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that is claimed by appellants. For example, the examiner has not explained what motivation the ordinary artisan would have had to use an ink-jet in conjunction with a test tube as described by Rutner instead of in conjunction with a plastic carrier sheet as described by Deeg. Furthermore, as noted by the examiner (answer, p. 13), the claimed invention is not limited to specific quantities of sample [or reagents] and the examiner has not pointed to evidence of advantages associated with using "larger quantities of reagents."

Therefore, based on this record, we conclude that the examiner has not established a prima facie case of obviousness and reverse the rejections of claims 1-4, 7-17 and 20-54 under 35 U.S.C. § 103(a) over Deeg in view of Rutner alone and/or further in view of Freundlich, Ohman, Mair, Rabitzsch, Diamandis and/or Xu.

OTHER MATTERS

Both of appellants' device claims (15 and 40) recite an analyte specific component immobilized on the surface of the reaction well, "either directly or via secondary immobilizing reagents." Appellants' method claims on the other hand all recite an analyte specific component immobilized "directly on a reaction well" or "on a solid phase attached to a reaction well." Upon return of this application to the jurisdiction of the examiner, the examiner should consider whether "secondary immobilizing reagents" and "a solid phase attached to a reaction well" are equivalent

terms which are both supported by appellants' specification within the meaning of 35 U.S.C. § 112, first paragraph, and take whatever action, if any, is appropriate.

CONCLUSION

To summarize, the decision of the examiner (I) to reject claims 1-4, 7-9, 15-17, 20-22, 28-34, 40-45 and 51-54 under 35 U.S.C. § 103(a) over Deeg in view of Rutner, (II) to reject claims 14, 27, 39 and 50 under 35 U.S.C. § 103(a) over Deeg in view of Rutner as applied to claims 1-4, 7-9, 15-17, 20-22, 28-34, 40-45 and 51-54 above, and further in view of Freundlich taken with each of Ohman, Mair and Rabitzsch, and (III) to reject claims 10-13, 23-26, 35-38 and 46-49 under 35 U.S.C. § 103(a) over Deeg in view of Rutner as applied to claims 1-4, 7-9, 15-17, 20-22, 28-34, 40-45 and 51-54 above, and further in view of Freundlich in view of Diamandis and Xu is **reversed**.

REVERSED

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RICHARD TORCZON	)
Administrative Patent Judge	)
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_____	) BOARD OF PATENT
CAROL A. SPIEGEL	) APPEALS AND
Administrative Patent Judge	) INTERFERENCES
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SALLY GARDNER-LANE	)
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APPENDIX

1. A method for performing a non-competitive heterogeneous immunoassay comprising an analyte specific component, an insulating layer, and a fluorescently labelled analyte specific component comprising the steps of

(a) immobilizing said analyte specific component 1) directly on a reaction well or 2) on a solid phase attached to a reaction well wherein said analyte specific component is in a single continuous region of said reaction well,

(b) adding an insulating layer which separates the analyte specific component from the labelled analyte specific component, which labelled analyte specific component can be antibodies or antigens, before drying,

(c) adding said labelled analyte specific component,

(d) drying said analyte specific component, said insulating layer, and said labelled analyte specific component in said reaction well,
followed by the steps of:

(e) adding a sample containing an unknown amount of the analyte to be analyzed,

(f) allowing said analyte to react with said analyte specific component and said labelled analyte specific component,

(g) washing said well following reaction of said analyte with said analyte specific component and said labelled analyte specific component, and

(h) detecting a signal from said labelled analyte specific component;

wherein all reagents other than said sample containing said analyte are added prior to step (e) and wherein said signal is a measure of said unknown amount of analyte in said sample.

2. A method for performing a non-competitive heterogeneous immunoassay comprising an analyte specific component, an insulating layer, and a fluorescently labelled analyte specific component comprising the steps of

(a) adding a sample containing an unknown amount of analyte to be

analyzed to a device comprising: (1) a reaction well; (2) an analyte

specific component immobilized directly on a reaction well or on a solid phase attached to said reaction well wherein said analyte specific component is in a single continuous region of said reaction well; (3) a labelled analyte specific component; and (4) an insulating layer which separates the analyte specific component from the labelled analyte specific component, wherein said analyte specific component immobilized on a solid phase, said labelled analyte specific component and said insulating layer have been dried in said well,

(b) allowing said analyte to react with said analyte specific component and said labelled analyte specific component,

(c) washing said well following reaction of said analyte with said analyte specific component and said labelled analyte specific component, and

(d) detecting a signal from said labelled analyte specific component,

wherein all reagents necessary to perform said noncompetitive immunoassay are immobilized or dried on said device prior to adding said sample and wherein said signal is a measure of said unknown amount of analyte in said sample.

15. A device for use in a non-competitive immunoassay comprising

(a) a reaction well,

(b) an analyte specific component immobilized on the surface of the reaction well, either directly or via secondary immobilizing reagents, wherein said analyte specific component is immobilized such that it will not wash off from said reaction well and wherein said analyte specific component is in a single continuous region of said reaction well,

(c) a fluorescently labelled analyte specific component, and

(d) an insulating layer that separates the analyte specific component from the labelled analyte specific component, in which device the analyte specific component, the labelled analyte specific component and the insulating layer all have been dried.

Independent claims 28, 29 and 40 recite corresponding method and device claims

for a competitive heterogeneous immunoassay.